REMARKS

The present Response is filed subsequent to an in-person interview with the Examiner, conducted on November 3, 2005, in which certain claim amendments presented herein were discussed, and the outstanding claim rejections resolved. Claims 1-4, 15, 17-22, 26, 30-33, and 36 have been amended, and new claims 49-53 added. Claims 40-48 were previously withdrawn. Upon entry of this amendment, claims 1-39 and 49-53 are presently pending.

The present Supplemental Amendment and Response is also being filed to clarify certain amendments made in Applicants' prior Response to the first Office Action, which was timely filed on October 5, 2005 (the same amendments were reflected in their Response to Non-Compliant Amendment as well, timely filed on October 20, 2005). In their prior Responses, Applicants errantly and unknowingly filed a Listing of Claims that corresponded to the parent application (Attorney Docket No. CST-201) of the present case. Accordingly, Applicants have for clarity and convenience re-presented those amendments herewith, together with new amendments, as reflected in the current complete (and correct) Listing of the Claims. Applicants request that the present amendments (to the claims as originally filed) be entered in their entirety, and that the previously filed claim amendments not be entered.[1]

Claim 1 has been amended to more distinctly point out the characteristics and features of the claimed subject matter. More particularly, claim 1 has been amended to clarify that the method of the invention isolates a "population of naturally-occurring post-translationally" modified peptides. Dependent claims 2, 4, 15, 19-22, and 26 have accordingly been amended reflect the amendment to independent claim 1. Dependent claim 15 has also been amended to clarify that the antibody "specifically binds" the recited preferred motifs.

Dependent claims 3, 18, 32, and 36 have been amended to provide the full names of certain abbreviations recited in the claims. Dependent claim 17 has been amended to clarify that the motif "consists of" all or part of the recited motifs.

Claim 30 has been amended to more distinctly point out the characteristics and features of the claimed subject matter. More particularly, claim 30 has been amended to clarify that this preferred method of the invention isolates a "population of" phosphopeptides. Dependent claim 31 has

[1] However, Applicants do request that their previously filed Remarks and arguments be entered into the record in their entirety.

accordingly been amended reflect the amendment to independent claim 30, and to correct a typographical error.

Claims 32 and 33 have been amended to correct a typographic error and now properly rely on independent claim 30, on which they depend.

Lastly, new dependent claims 49-53 have been added and are drawn to certain preferred embodiments of the method of claim 1. More particularly, new dependent claims 49-52 (which are substantially identical to existing dependent claims 37-39 (which themselves rely on claim 30)), are drawn to additional steps of the method that may preferably be employed. New dependent claim 53 recites certain preferred post-translational modification specific antibodies within the scope of the invention, namely those that specifically bind a "a single modified amino acid selected from the group consisting of an acetylated amino acid, a glycosylated amino acid, and a methylated amino acid."

These amendments are supported throughout the specification and claims as originally filed, for example, at p. 1, lines 14-21; p. 6, lines 12-23; p. 7, lines 22-29; p. 19, lines 9-18; p. 20, lines 13-18; p. 21, lines 7-15; p. 25, lines 4-16; p. 26, lines 11-28; p. 34 lines 5-27; p. 53, lines 4-28, and the Examples. The present amendments do not introduce new matter.

SUMMARY OF INTERVIEW

Applicants thank the Examiner for the courtesy of the in-person interview conducted on November 3, 2005. Also present at the interview, in addition to the Examiner and Applicants' attorney, were Primary Examiner Bao Thuy Nguyen (Art Group 1641), Dr. John Rush, Ph.D. (the first named inventor on the present application, and a person of skill in the art to which the invention pertains), and Mr. Andrew Warner, J.D. (a patent agent assisting Applicants' attorney with this case).

During the interview, Applicants discussed the state and shortcomings of the art existing at the time the present application was filed, and how these shortcomings were solved by the method of the invention. Several prominent review articles (all but one already of record) establishing the state of the art were discussed. These references, which are further discussed below, clearly evidence the failures of the prior art to provide a suitable method for the selective isolation of post-translationally modified peptides as presently claimed and teach away from the present invention. These references support the novelty and non-obviousness of the presently claimed subject matter. The limitations of the primary reference, Little *et al.* (U.S. Pat. No. 6,322,970), were also discussed, and the disclosure

of this reference distinguished from the present invention, as further described below. Certain claim amendments presented herein were discussed, which amendments more distinctly point out the characteristics and features of the claimed subject matter, as distinguished from the limited teachings of Little.

At the conclusion of the interview, the Examiner agreed that the arguments and amendments presented herein distinguish the claimed invention from the prior art, including the disclosure of Little (and the secondary references (discussed below) that rely on Little), and that the present claims would be allowable upon entry of this Amendment & Response.

STATE OF THE ART – MANN, MARCUS, QUADRONI & CONRADS REFERENCES

During the interview, Applicants' attorney and Dr. John Rush discussed several review articles establishing the state of the art at the time the present invention was filed. These references (along with other prior art discussed in the Background of the specification) evidence the novelty and non-obviousness of the presently claimed subject matter. Specifically, the following references were discussed: Mann *et al., Trends in Biotech. 20:* 261-268 (2002) (cited and discussed in the Background (Ref. CG)) (hereinafter "Mann"); Marcus *et al., Electrophoresis 21:* 2622-2636 (2000) (cited and discussed in the Background (Ref. CF); Quadroni *et al.*, "Phosphopeptide Analysis", *Proteomics in Functional Genomics 88:* 199-213 (2000) (presently provided by Supplemental IDS herewith as Ref. DA); and Conrads *et al., Nat. Biotech. 23:* 36-37 (Jan. 2005) (Ref. CZ of record).

Mann (Ref. CG) is a review of peptide isolation and phosphoproteomic mass spectrometry approaches authored by one of the recognized leader in the field to which the present invention relates. As discussed by Dr. Rush in the interview, this review represents and expressly states the prevailing view (at the time the present application was filed) that phospho-specific antibodies were *not* suitable for selectively isolating phosphorylated peptides from mixtures, due to various technical limitations.

Marcus (Ref. CF) is an article describing the study of tyrosine-phosphorylated proteins using mass spectrometric techniques and anti-phosphotyrosine antibodies. As discussed by Dr. Rush in the interview (and noted in the Background of the specification at p. 4), the paper expressly concludes that the detection of phosphorylation sites (phosphopeptides) using such an antibody is "almost impossible" due to various technical limitations, including binding affinity. *See Marcus* p. 2635, end of 3.2.1.

Quadroni (Ref. DA, presently submitted) is a review article of phosphopeptide analysis techniques discussing and representing the state of the art around the time of the present invention. As discussed by Dr. Rush in the interview, the paper, in discussing the use of anti-phospho amino acid antibodies to immunoaffinity isolate phosphopeptides, expressly states that "As a general rule, all these antibodies behave quite poorly as affinity reagents, especially bad towards small peptides, and their main application remains in Western blotting." *See* Quadroni at p. 201, end of 1.3. The paper also expressly states that attempts to use anti-phosphotyrosine antibodies to isolate phosphotyrosine-containing peptides had failed.

In the interview, Dr. Rush stated that the present invention was in fact a novel and surprising advance over prior approaches, since the prior art, including publications like Mann, Marcus, and Quadroni, clearly taught away from the suitability of using post-translational modification-specific antibodies to immunoaffinity isolate target post-translationally modified peptides. As also noted in the interview, the novelty of the present invention is underscored by the surge of commercial and academic interest in Applicants' invention. For example, to date, almost every major international pharmaceutical company has initiated pilot projects with the Assignee of the present invention to access the technology for drug development purposes, and several major academic phosphoproteomics leaders, like Harvard University and U.C.L.A., have either licensed the technology or expressed interest in doing so.

Dr. Rush also discussed, during the interview, that the novelty of the present invention is further underscored by Conrads (Ref. CZ), a review article of Applicants' method that appeared in the leading journal, *Nature Biotechnology*, shortly after Applicants published an article about their method (following the filing of this application). In the review, the authors expressly conclude that the Applicants' invention "address[es] the deficiency" in prior art proteomics approaches for isolating phosphopeptides, and go on to highlight several of the problems (*e.g.* low abundance of phosphopeptides from complex mixtures, need for enrichment, etc.) with prior art approaches that remained unsolved until the Applicants' invention.

NOVELTY REJECTIONS BASED ON LITTLE

The Examiner has previously rejected claims 1-3, 9-12, 19, 20, 22-24, and 27 under 35 U.S.C. §102(e) as allegedly being anticipated by Little *et al.* (U.S. Pat. No. 6,322,970, "Mass Spectrometric Detection of Polypeptides" (issued Nov. 27, 2001) (hereinafter "Little")).

As discussed at length in the interview, Little discloses no more than a method for expressing a single protein of interest *in vitro*, and then selectively isolating the target protein (or peptide) of interest by either (i) introducing an artificial tag (such as the His-tag or Biotin) to the target protein and then isolating it using an artificial tag-specific antibody or (ii) using a traditional target protein-specific antibody (e.g. a sequence-specific antibody) to isolate the single desired target protein. Little fails to describe or enable a method for selectively isolating, from a complex mixture of peptides, a population of naturally-occurring post-translationally modified peptides by using an antibody that specifically binds a naturally-occurring post-translationally modified amino acid or motif. Indeed, as discussed in the interview, such reagents were generally unavailable at the time of Little.

In contrast, as discussed in the interview, the method of the present invention provides for the selective isolation, from a complex mixture, of *a population* of *naturally-occurring* (*i.e.* in vivo) post-translationally modified peptides using an antibody that specifically binds a desired post-translationally modified amino acid or motif that recurs in a *multitude of different peptides*. The method of the invention, therefore, is capable of isolating, from a complex mixture, a great number of different peptides that contain a naturally occurring post-translationally modified amino acid (or motif) of interest, and is suitable, *e.g.*, for obtaining a "snapshot" of cell wide peptide modification *in vivo*. *See, e.g.*, Specification at p. 19, lines 9-19.

As discussed in the interview, the novelty of the presently claimed subject matter over the prior art, including Little, is underscored by references like Mann, Marcus, Quadroni, and Conrads, all of which teach away from the present invention and clearly evidence that Applicants have provided a solution to a long-standing need that is both novel and patentable. Indeed, if Little had in fact disclosed the presently claimed subject matter, Applicants would not have experienced the surge of commercial and academic interest in the present invention that has occurred.

Accordingly, Applicants submit that the presently claimed subject matter is novel and patentable over Little. In order to more distinctly point out the characteristics and features of the claimed invention, Applicants have amended claim 1 (and certain dependent claims) – as discussed in the interview – to recite that the method provided by the invention isolates "a population of naturally-occurring" post-translationally modified peptides from a complex mixture of peptides. Applicants respectfully submit that claims 1-3, 9-12, 19, 20, 22-24, and 27 (as well as the other pending claims), as amended, are patentable over Little, and respectfully request that these novelty rejections be withdrawn.

OBVIOUSNESS REJECTIONS BASED ON LITTLE

The Examiner has rejected claims 12-16, 30, 32, and 34 under 35 U.S.C. §103(a) as allegedly being obvious given Little (U.S. Pat. No. 6,322,970; *see supra.*) in view of various secondary references (Pidgeon and Goshe) as further discussed below).

As discussed in the interview, the primary reference, Little, fails to teach, suggest, or make obvious Applicants' invention as presently claimed. The limited teachings of Little, and how the method it discloses is distinguished from the present invention, are described above. As acknowledged by the Examiner during the interview, because the primary reference, Little, fails to render obvious the invention as most broadly claimed in independent claims 1 and 30, the claim rejections based on combinations of Little and various secondary references similarly fail. Accordingly, Applicants respectfully submit that the subject matter of claims 4, 7, 8, 12, 13-18, 21, 29, and 30-34 (as well as all other pending claims) is non-obvious and patentable over Little and the cited secondary references, and respectfully request that these rejections be withdrawn.

Further, as discussed during the interview, neither of the secondary references – Pidgeon (U.S. Pat. No. 6,579,720, (issued June 17, 2003)) or Goshe (U.S. Pat. No. 6,818,970, (issued November 16, 2004)) – taken alone or combined with Little, teach, suggest, or make obvious the presently claimed methods for selectively isolating, from a complex mixture, a population of naturally-occurring post-translationally modified peptides by immunoaffinity isolation using a post-translational modification-specific antibody.[2] Indeed, the nonobviousness of the present invention over the prior art is evidenced by references like Mann, Marcus, Quadroni, and Conrads, discussed above, as well as the surprising results, long-felt but unsolved need, and commercial success associated with the invention, as discussed during the interview by Dr. John Rush and Applicants' attorney.

§112, 2ND PARAGRAPH, INDEFINITENESS REJECTIONS

The Examiner has previously rejected claims 1, 3, 7, 18, 30, 32, and 36 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite.

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[2] The limited teachings of Goshe and Pidgeon were discussed at length in Applicants' Response to the first Office Action. Neither of these references, or any of the additional references cited in the parent case of the present application, cures the deficiencies of Little.

APPLICANTS: Rush *et al.*
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Applicants have amended claims 3, 18, and 36 to provide the full names of certain abbreviations recited in the claims. Applicants respectfully submit that the rejection of the remaining claims (including claims 1 and 7) has been obviated based on arguments presented in their prior Response (during the interview, the Examiner acknowledged this point), and that these claims are clear and definite to those of skill in the relevant art. Accordingly, Applicants respectfully request that the indefiniteness rejection of theses claims be withdrawn.

DOUBLE-PATENTING (STATUTORY) REJECTIONS

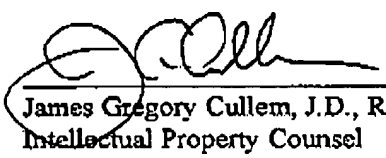
The Examiner has maintained the provisional rejection of claims 1-29 under 35 U.S.C. §101 for "statutory" double patenting, as allegedly claiming the same invention as that of claims 1-29 of co-pending application USSN 10/174,486 (Rush *et al.* -- also owned BY CELL SIGNALING TECHNOLOGY, INC., the assignee of the present application).

Since the rejection is provisional, Applicants respectfully renew their request that this rejection be held in abeyance until such time as the present application or cited co-pending application issues as a patent, at which time Applicants will cancel or amend any identical claims in the remaining application.

Conclusion

As acknowledged by the Examiner during the interview, the present claims are patentable over the prior art, and believed to be in condition for immediate allowance. Reconsideration and withdrawal of the outstanding rejections is respectfully requested, and early and favorable allowance of these claims is earnestly solicited. If there are any questions regarding these amendments and remarks, the Examiner is requested to call the undersigned attorney at the telephone number provided.

Respectfully submitted,



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Date: November 9, 2005